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10/580,458	05/24/2006	William Vainchenker	065691-0445	1466

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,458	VAINCHENKER ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 29-42* is/are pending in the application.

4a) Of the above claim(s) *5-7,10-23,27 and 32-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,24-26,29-31 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *May 24, 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of April 1, 2009, in response to the Action of October 2, 2008, is acknowledged. It is acknowledged that Claim 28 has been cancelled and Claims 1-4, 8, 9, 24-26, 29-31, and 42 have been amended. Claims 1-27 and 29-42 are pending. Claims 5-7, 10-23, 27, and 32-41 were withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 1-4, 8, 9, 24-26, 29-31, and 42 are hereby reexamined.

Drawings-Objections

Objection to Figure 1 because the legend thereto states it is a representation of the role of JAK2 in PV; however, the term PV fails to occur in said figure is maintained. Applicants have not filed a replacement Fig. 1.

Objection to Figure 9 because the lanes are not labeled or explained is maintained. Applicants have not filed a replacement Fig. 9.

Specification-Objections

Objection to the legends to Figures 2, 3, 5, 9, and 10 because they fail to clearly explain the data of the figures is maintained. Objection to the legend to Figure 5 because it fails to explain the two panels is maintained. Applicants did not comment on theses objections.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Rejection of Claim 4 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is maintained. The mammalian cell of Claim 4 is likely to occur in

nature, therefore the recited subject matter fails to show the "hand of man". It is suggested that the claims be amended to recite "isolated" or "recombinant".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 8, 9, 24-26, 29-31, and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Rejection of Claims 1-4, 29-31, and 42, because the phrase "JAK2" renders the claims indefinite, is maintained. Applicants did not remark on this rejection. Nonetheless, the examiner makes the following comments regarding the claims, as amended. In Claim 1, the phrase "JAK2 protein" implies that the recited protein has the function of a JAK2 protein. As explained in the prior action, the specification describes JAK2 proteins in a manner that fails to define the function(s) of the encompassed proteins. Moreover, since the protein of SEQ ID NO: 1 is a variant of the normal human JAK2 protein and the variant is associated with Vaquez polyglobulia, it is unclear that said variant has the desired "JAK2" activity. The skilled artisan cannot be apprised of the metes and bounds of the functional limitations of Claim 1 and claims dependent therefrom.

Rejection of Claims 1-4, 29-31, and 42 because in Claim 1 "comprising the V617F mutation" in combination with "sequence shown in SEQ ID NO: 1" renders the claims indefinite, is maintained. As explained in the prior actions, it is unclear whether said phrase

means the JAK2 kinase is (i) the sequence of SEQ ID NO: 1 or (ii) the sequence of SEQ ID NO: 1 with a Phe substitution at residue at 617.

For Claim 1 the term "having" renders the claim indefinite. It is unclear whether said term means comprising or consisting of. Claims 2-4, 29-31, and 42 , as dependent from Claim 1, are indefinite for the same reason.

Regarding the three above rejections, it is suggested that Claim 1 be amended to use the following type of language: --An isolated variant of human JAK2 (Janus kinase 2) protein, wherein the variant has a V617F mutation and has the sequence shown in SEQ ID NO: 1.--

Rejection of Claims 8, 9, and 24-26 because, as explained in the prior action the phrase "position 1849" renders the claims indefinite, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The specification explains the location and nature of the mutations in SEQ ID NO 3 and SEQ ID NO 4 relevant to the polynucleotide of SEQ ID NO: 2. These arguments are not found to be persuasive for the following reasons. It is applicants' duty to clearly recite their invention. In the instant case, applicants have left to the public the burden of searching through the specification to try to understand, and make assumptions on, the invention of Claims 8, 9, and 24-26. Nonetheless, the specification appears to have sufficient support for incorporating into the claims the residues of SEQ ID NO: 3 and 4 that correspond to "position 1849" of SEQ ID NO: 2. Said incorporations will allow the Office to search the recited invention.

Rejection of Claims 24-26, and 29, because the phrases "G1849T" and "t^{1849}" render the claims indefinite, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The specification clearly explains the phrase

"G1849T mutation" as recited in claim 25 and "mutated t1849 nucleotide" as recited in claim 29. These arguments are not found to be persuasive for the following reasons. It is applicants' duty to clearly recite their invention. In the instant case, applicants have left to the public the burden of searching through the specification to try to understand, and make assumptions on, the invention. Any claim reciting an amino acid or nucleotide residue must also recite a sequence identifier number (SEQ ID NO:) in order to comply with 35 U.S.C. 112, second paragraph. Recitation of a sequence identifier number will allow the Office to search the recited invention.

Claims 1-4, 8, 9, 24-26, 29-31, and 42 are indefinite for improper antecedent usage as follows.

For Claim 1, "the V671F mutation" lacks antecedent basis. Claims 2-4, 29-31, and 42, as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph for the same reason.

For Claim 8, "the mutated nucleotide t1849" lacks antecedent basis.

Rejection of Claim 9, because the phrase "Probes or primers according to claim 8" should be corrected to "The probes or primers according to claim 8", is maintained.

For Claims 24-26 and 29, the phrase "the JAK2 V617 variant" lacks antecedent basis.

Rejection of Claim 26, because the phrase "Kit according to claim 24" should be corrected to "The kit according to claim 24", is maintained.

For Claims 30-31 and 42, the phrases "An siRNA according to claim 29" and "A siRNA according to claim 29" should be corrected to "The siRNA according to claim 29".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 1-4, 8, 9, 24-26, 29-31, and 42 under 35 U.S.C. 112, first paragraph/enablement, for essentially the same reasons explained in the prior action, is maintained. Based on amendment, the following additional comments are made. The specification does not reasonably provide enablement for (i) any protein comprising SEQ ID NO: 1 and having any "JAK2 activity" or any encoding polynucleotide (Claims 1-4) or (ii) any probe, primer, or siRNA derived from SEQ ID NO: 3, 4, 11, and 29-31 and having a mutation at "1849" (Claims 8, 9, 24-26, 29-31, and 42). It is noted that by use of "comprising" language, Claims 1-4 encompass polypeptides/polynucleotides, wherein the desired activity is not derived from the sequence homologous to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims have been previously compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability

or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation. Nonetheless, the following additional comments are made.

The specification does not support the broad scope of Claims 1-4, 8, 9, 24-26, and 28-31 because the specification does not establish: (A) the desired "JAK2" function for all proteins comprising SEQ ID NO: 1; (B) regions of all proteins comprising SEQ ID NO: 1 which may, or may not, be modified without affecting the desired activity; (C) the general tolerance of the desired "JAK2" activity to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; (E) any probes, primers, or siRNAs derived from SEQ ID NO: 3, 4, 11, or 29-31 and having a mutation at "1849"; (F) the desired activity of any probes or primers derived from SEQ ID NO: 3, 4, 11, and 29-31 and having a mutation at "1849"; (G) regions of any probes, primers, or siRNAs which may, or may not, be modified without affecting the desired activity; (H) the identity of siRNAs derived from SEQ ID NO: 3, 4, and 11, and having a mutation at "1849", wherein the siRNA can be used for (i) reducing expression of any "JAK2 V617F" by more than 50% or (ii) reducing expression of any "JAK2 V617F" by more than 80%, while reducing expression of any wild type "JAK2" by only 25%. and (I) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to successful for attaining the desired utility.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including (i) any protein comprising SEQ ID NO: 1 and having any JAK2 activity or any encoding polynucleotide or (ii) any probe, primer, or siRNA derived from SEQ ID NO: 3, 4, 11, and 29-31 and having a mutation at "1849". The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection be withdrawn, Applicants provide the following arguments, which are relevant here.

(A) Applicants have obviated this ground of rejection by amending claim 1 to a protein "having the sequence shown in SEQ ID NO 1". The Office acknowledged enablement for this scope.

(B) Applicants could not find any specific reference in the Office's non-enablement rejection (Office Action, pages 10-13) regarding why claim 8 is not enabled.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that Claim 1 is so amended. However, as explained above, Claims 1-4 encompassed any protein comprising SEQ ID NO: 1 and having any "JAK2 activity" or any encoding polynucleotide. As explained above, by use of "comprising" language, Claims 1-4 encompass polypeptides/polynucleotides, wherein the desired activity is not derived

from the sequence homologous to SEQ ID NO: 1. As explained above under 35 USC 112, second paragraph, the phrase "JAK2 protein" in Claim 1 implies that the recited protein has the function of a JAK2 protein. However, the specification describes JAK2 proteins in a manner that fails to define the function of the encompassed proteins. Thus, the specification fails to enable the skilled artisan to make and use any protein comprising SEQ ID NO: 1 and having any JAK2 activity or any encoding polynucleotide.

(B) Reply: The prior action states the following.

(i) The specification does not reasonably provide enablement for any protein having a V617F mutation, wherein the protein has any structure and any or no function, encoding polynucleotides, or any probes, primers, or siRNAs thereof (pg 10, last parg).

(ii) The specification fails to enable the skilled artisan to make and use the subject matter of Claims 2, 3, 8, 9, 24-26, and 29 because the metes and bounds of said subject matter is unclear (pg 1, parg 3).

(iii) The specification does not support the broad scope of Claims 1-4, 8, 9, 24-26, and 28-31 because the specification does not establish: ...(G) the metes and bounds of the subject matter of Claims 1-4, 8, 9, 24-26, and 28-31; (H) a use for reducing the expression of SEQ ID NO: 2 and the siRNA molecules capable of affecting said reducing; (parg brding pg 12-13).

(iv) Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of "JAK2" polypeptides, variants thereof, encoding polynucleotides, and probes, primers, and siRNA molecules thereof (pg 13, last parg).

For these reasons and those explained in the prior action, rejection of Claims 1-4, 8, 9, 24-26, 29-31, and 42 under 35 U.S.C. 112, first paragraph/enablement, is maintained.

Written Description

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of proteins comprising SEQ ID NO: 1 and having any "JAK2 activity" or any encoding polynucleotide. The specification teaches the structure of no proteins comprising SEQ ID NO: 1 and having any "JAK2 activity" or any encoding polynucleotide. Moreover, the specification fails to describe any representative species by any identifying characteristics or properties other than the functionality of having any "JAK2 activity". Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Rejection of Claims 24-26, and 29 under 35 U.S.C. 112, first paragraph/written description, because the metes and bounds of the recited invention is unclear and, thus, it is unclear whether Applicants were in full possession of the claimed subject matter, is maintained. Claims 30 and 31, as amended to be dependent from Claim 29, are herein rejected under first paragraph/written description, for the same reason.

Claim 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of siRNA molecules capable of (i) reducing expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by more than 50% or (ii) reducing expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by more than 80%, while reducing expression of any wild type "JAK2" by only 25%. The specification teaches the structure of only three representative species of (i) and no representative species of (ii). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of capable of (i) reducing expression of any "JAK2 V617F" by more than 50% or (ii) reducing expression of any "JAK2 V617F" by more than 80%, while reducing expression of any wild type "JAK2" by only 25%. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In support of their request that the prior rejections be withdrawn, Applicants provide the following arguments, which are relevant here.

(C) The Office has not explained why the disclosure of three representative species of siRNA in the specification is insufficient to show possession of the full scope of the invention.

(D)The skill artisan can turn to computer programs to generate additional suitable siRNAs for a given nucleotide sequence.

These arguments are not found to be persuasive for the following reasons.

(C) Reply: It is acknowledged that the specification discloses three siRNA molecules capable of reducing expressing of the recombinant protein of SEQ ID NO: 1 expressed in host cells. However, the specification fails to disclose any siRNA molecules capable of reducing expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by more than 80%, while reducing expression of any wild type "JAK2" by only 25%. In addition, the specification fails to disclose any siRNA molecules capable of reducing expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by 50%.

(D) Reply: It is acknowledged that computer programs are available for predicting useful siRNA molecules. However, trial and error testing of an essentially unlimited number of predicted siRNA molecules, in any assay system, for the ability to (i) reduce expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by more than 50% or (ii) reduce expression of any "JAK2 V617F" comprising SEQ ID NO: 1 by more than 80%, while reducing expression of any wild type "JAK2" by only 25% represents undue experimentation.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
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